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(54) Title: PROCESSES FOR PREPARING QUINOLONECARBOXYLATE DERIVATIVES

(57) Abstract: The present invention provides a process for preparing quinolonecarboxylate derivatives under a mild condition in high yield, so as to be favorably applied to a large-scale mass production thereof.

PROCESSES FOR PREPARING QUINOLONECARBOXYLATE DERIVATIVES

Technical Field

The present invention relates to a process for preparing quinolonecarboxylate derivatives, which are useful as an intermediate for the preparation of quinolone anti-bacterial agents.

Background Art

Quinolonecarboxylate derivatives are useful as an intermediate for the preparation of various quinolone anti-bacterial agents, including sparfloxacin, gemifloxacin, trovafloxacin, ciprofloxacin, temafloxacin, fleroxacin, and levofloxacin.

Conventional processes for preparing quinolonecarboxylate derivatives includes a quinoline-ring forming step (i.e., cyclization step), which is performed in the presence of a base such as potassium carbonate or sodium hydride (see US Pat. No. 5,639,886; *J. Med. Chem.*, 1989, 32, 1313-1318; WO 00/50428; US Pat. No. 4,795,751; JP Publication No. 89/100165; US Pat. No. 4,730,000; *J. Med. Chem.*, 1986, 29, 2363-2369; and US Pat. No. 4,777,253).

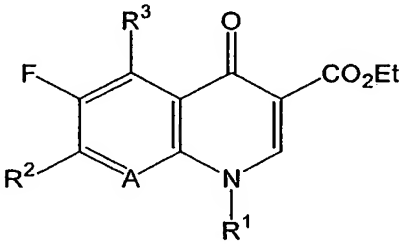
Potassium carbonate is commercially available in form of granules. However, when granular potassium carbonate is used in a reaction for cyclizing a quinoline-ring, the reaction cannot be completed and the yield is very low, about 20 ~ 30 %. Therefore, in order to complete the reaction, granular forms of potassium carbonate need to be reduced to powder, which requires an additional process, excess amounts of potassium carbonate (about 3 – 5 eq.), and/or equipment for grinding the granules in a reactor. Further, when a reaction is performed in high temperature using potassium carbonate, carbon dioxide (CO_2) gas is produced, which makes the process dangerous. Accordingly, potassium carbonate has difficulties to be applied to an industrial-scale mass production.

Meanwhile, sodium hydride is very sensitive to water, which makes the reaction violent and dangerous (e.g., a possibility of explosion). Further, the yield thereof shows very high variation, about from 50 to 90%, so that it is also difficult to be applied to an industrial-scale mass production.

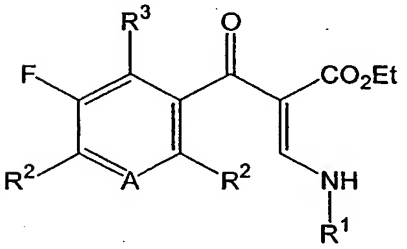
Disclosure of the Invention

The present invention provides a process for preparing quinolonecarboxylate derivatives under a mild condition in a high yield, so as to be favorably applied to a large-scale mass production.

In one aspect of the present invention, there is provided a process for preparing a compound of formula (I) or its salt, which comprises reacting a compound of formula (II) with potassium phosphate tribasic (K_3PO_4) in an orgarnic solvent:



(I)



(II)

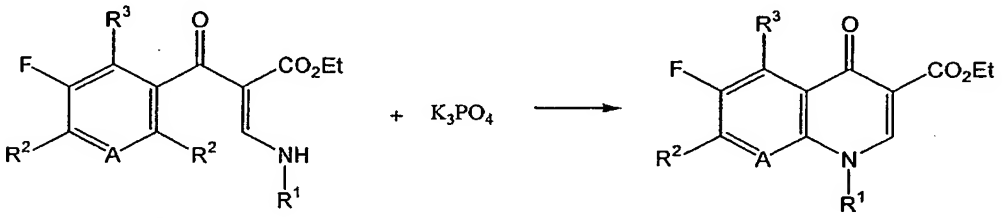
wherein, R^1 is cyclopropyl, 2,4-difluorophenyl, or 1-acetoxyprop-2(S)-yl; R^2 and R^3 are independently hydrogen, chloro, or fluoro; and A is CH, CF, CNO_2, or N.

The above and other features and advantages of the present invention will become more apparent by describing in detail a preferred embodiment thereof.

Best mode for carrying out the Invention

In accordance with one aspect of the present invention, quinolonecarboxylate derivatives are prepared in high yield by reacting a compound of formula (II) with K_3PO_4 in an orgarnic solvent. The resulting compound may be further purified and isolated. This process may be illustrated as the following reaction scheme 1.

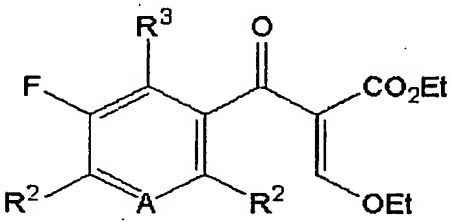
Reaction scheme 1



(II) (I)

In the above reaction scheme 1, A, R^1, R^2, and R^3 are the same as defined above.

The compound of formula (II) may be prepared by a method which is known in the art (US Pat. No. 5,237,060). For example, the compound of formula (II) may be prepared by reacting a compound of the following formula (III) with amine derivatives (NH_2-R^1) in an organic solvent such as dichloromethane, alcohol, chlororform, cyclohexane or toluene. The reaction may be performed at 20 ℃ ~ 25 ℃.



(III)

In the compound of formula (III), A, R^2 and R^3 are the same as defined above.

The compound of formula (III) may be prepared by a method which is known in the art (*J. Med. Chem.*, 1986, 29, 2363; *J. Org. Chem.*, 1970, 35, 930; *Organicum*, 3rd edition, 1964, 438; and US Pat. No. 5,237,060).

In the process of the present invention, potassium phosphate tribasic may be used in an excess amount, i.e., about 1.5~2.8 eq., preferably 1.5~2.0 eq. to 1 eq. of the compound of formula (II), so as to obtain the product in high yield. In case that potassium phosphate tribasic is used less than 1.5 eq. to 1 eq. of the compound of formula (II), the compound of formula (II) may remain un-reacted.

The process of the present invention may be performed in the presence of various organic solvents, including methyl alcohol, ethyl alcohol, isopropyl alcohol, methylene chloride, dichloroethane, chloroform, acetone, methyl ethyl ketone, ethyl acetate, methyl acetate, toluene, benzene, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and etc. Among them, a solovent useful for the present invention preferably includes acetonitrile methyl ethyl ketone, ethyl acetate, ethyl alcohol, dichloroethane and toluene, more preferably includes acetonitrile.

Although a higher temperature may increase a reaction rate, the reaction may be performed at 60°C ~ 82°C, preferably at 75°C ~ 80°C, to obtain the product in high purity and yield. The reaction may be performed in about 1 ~ 12 hours, preferably about 1 ~ 3 hours.

The process of the present invention may further comprise a step for purifying in order to remove any by-product, e.g., potassium phosphate dibasic. The purifying step may be performed according to conventional methods. For example, the reaction mixture obtained in the above is filtered, preferably under a reduced pressure. An organic solvent, such as dichloromethane, ethyl acetate, or a mixture thereof, is added to the concentrate of the resulting filtrate, followed by washing with water. The resulting organic layer is concentrated to obtain a purified product, i.e., the compound of formula (I).

By using potassium phosphate tribasic according to the present invention, quinolonecarboxylate derivatives of formula (I) can be prepared under a mild condition in high yield, so as to be favorably applied to a

large-scale mass production thereof. Further, using 3-quinolonecarboxylate derivatives obtained according to the process of the present invention, various intermediates for the preparation of quinolone anti-bacterial agents, including sparfloxacin, gemifloxacin, trovafloxacin, ciprofloxacin, temafloxacin, fleroxacin, levofloxacin, or etc., can be favorably prepared under a mild condition in large-scale mass production.

The present invention is further illustrated and described by the following examples, which should not be taken to limit the scope of the invention.

Example 1:

Preparation of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate

3.0 g of ethyl 3-cyclopropylamino-2-pentafluorobenzoyl acrylate was dissolved in 15 ml of acetonitrile under heating to 75 ~ 80 ℃. 3.28 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 30 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 30 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 2.74g of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 96.9 %).

^{1}H NMR ($CDCl_3$, ppm) : 1.17(4H, m, CH_2CH_2), 1.39(3H, t, J=8, CH_2CH_3), 3.88(1H, m, NCH), 4.37(2H, q, J=8, CH_2CH_3), 8.48(1H, s, C2-H)

Example 2:

Preparation of ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate

7.0 g of ethyl 3-cyclopropylamino-2-(2,6-dichloro-5-fluoropyridine-3-carbonyl)acrylate was dissolved in 35 ml of acetonitrile under heating to 75 ~ 80 ℃. 8.56 g (2.0 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 77 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 77 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 6.17g of ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Yield: 98.5 %).

^{1}H NMR($CDCl_3$, ppm) : 1.20(4H, m, CH_2CH_2), 1.41(3H, t, J=8, CH_2CH_3), 3.66(1H, m, NCH), 4.41(2H, q, J=8, CH_2CH_3), 8.44(1H, d, J=4, C5-H), 8.66(1H, s, C2-H)

Example 3:

Preparation of ethyl 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate.

6.0 g of ethyl 2-(2,6-dichloro-5-fluoropyridine-3-carbonyl)-3-(2,4-difluorophenylamino)acrylate was dissolved in 30 ml of acetonitrile under heating to 75 ~ 80 ℃. 5.47 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 66 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 66 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 5.25 g of ethyl

1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Yield: 95.8 %).

^{1}H NMR($CDCl_3$, ppm) : 1.41(3H, t, *J*=8, CH_2CH_3), 4.41(2H, q, *J*=8, CH_2CH_3), 7.12(2H, m, aromatic C5'- & C6'-H), 7.45(1H, m, aromatic C3'-H), 8.48(1H, d, *J*=8, C5-H), 8.55(1H, s, C2-H)

Example 4:

Preparation of ethyl 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate.

10.0 g of ethyl 2-(2-chloro-4,5-difluorobenzoyl-3-cyclopropylamino)acrylate was dissolved in 50 ml of acetonitrile under heating to 75 ~ 80 ℃. 18.03 g (2.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 2 hours. The reaction mixture was filtered under a reduced pressure and washed with 60 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 300 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 8.77 g of ethyl 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 98.7 %).

^{1}H NMR($CDCl_3$, ppm) : 1.26(4H, m, CH_2CH_2), 1.41(3H, t, *J*=8, CH_2CH_3), 3.44(1H, m, NCH), 4.39(2H, q, *J*=8, CH_2CH_3), 7.73(1H, m, C8-H), 8.25(1H, m, C5-H), 8.58(1H, s, C2-H)

Example 5:

Preparation of ethyl 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate.

8.0 g of ethyl 2-(2-chloro-4,5-difluorobenzoyl)-3-(2,4-difluorophenylamino)acrylate was dissolved in 80 ml of acetonitrile under heating to 75 ~ 80 ℃. 11.84 g (2.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 2 hours. The reaction mixture was filtered under a reduced pressure and washed with 40 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 88 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 6.69 g of ethyl 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 92 %).

^{1}H NMR($CDCl_3$, ppm) : 1.40(3H, t, *J*=8, CH_2CH_3), 4.39(2H, q, *J*=8, CH_2CH_3), 6.67(1H, m, C8-H), 7.20(2H, m, aromatic C5'- & C6'-H), 7.54(1H, m, aromatic C3'-H), 8.29(1H, d, *J*=8, C5-H), 8.38(1H, s, C2-H)

Example 6:
Preparation of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate.

8.0 g of ethyl 3-(2-fluoroethylamino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate was dissolved in 64 ml of acetonitrile under heating to 75 ~ 80 ℃. 9.06 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 80 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 48 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 7.29 g of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 96.9 %).

^{1}H NMR($CDCl_3$, ppm) : 1.41(3H, t, *J*=8, CH_2CH_3), 4.40(2H, q, *J*=8, CH_2CH_3), 4.60-4.89(4H, m, CH_2CH_2F), 8.20(1H, m, C5-H), 8.39(1H, s, C2-H)

Example 7:

Preparation of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate.

3.0 g of (+) ethyl 2-(2,4-dichloro-3-nitro-5-fluorobenzoyl)-3-[(1-acetoxyprop-2(S)-yl)amino]acrylate was dissolved in 15 ml of acetonitrile under heating to 75 ~ 80 ℃. 2.12 g (1.5 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 60 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 50 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 2.64 g of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate (Yield: 95.7 %).

^{1}H NMR($CDCl_3$, ppm) : 1.43 (3H, t, J=7.2, CH_2CH_3), 1.62(3H, d, J=6.8, $NCHCH_3$), 1.94(s, 3H), 4.13(1H, m, CH_2OAc), 4.31(1H, m, CH_2OAc), 4.43(3H, m, CH_2CH_3 & $NCHCH_3$), 8.45(1H, d, J=8.4, C5-H), 8.61(1H, s, C2-H)

Example 8

Preparation of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate

45.69 g of (+) ethyl 2-(2,4-dichloro-3-nitro-5-fluorobenzoyl)-3-[(1-acetoxyprop-2(S)-yl)amino]acrylate was dissolved in 270 ml of acetonitrile under heating to 70 ~ 75 ℃. 32.25 g

(1.5 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 4 hours. The reaction mixture was filtered under a reduced pressure and washed with 500 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 300 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 46.2 g of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate (Yield: 95.4 %).

Example 9.

Preparation of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate.

45.69 g of (+) ethyl 2-(2,4-dichloro-3-nitro-5-fluorobenzoyl)-3-[(1-acetoxyprop-2(S)-yl)amino]acrylate was dissolved in 270 ml of acetonitrile under heating to 65 ~ 70 ℃. 32.25 g (1.5 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 4 hours. The reaction mixture was filtered under a reduced pressure and washed with 500 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 300 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 45.4 g of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate (Yield: 93.7 %).

Example 10:

Preparation of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate.

45.69 g of (+) ethyl 2-(2,4-dichloro-3-nitro-5-fluorobenzoyl)-3-[(1-acetoxyprop-2(S)-yl)amino]acrylate was dissolved in 270 ml of acetonitrile under heating to 78 ~ 82 ℃. 32.25 g (1.5 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 500 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 300 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 46.0 g of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate (Yield: 95.0 %).

Example 11:

Preparation of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate..

45.69 g of (+) ethyl 2-(2,4-dichloro-3-nitro-5-fluorobenzoyl)-3-[(1-acetoxyprop-2(S)-yl)amino]acrylate was dissolved in 270 ml of acetonitrile under heating to 70 ~ 75 ℃. 32.25 g (1.5 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 12 hours. The reaction mixture was filtered under a reduced pressure and washed with 500 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 300 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 46.6 g of (-) ethyl N-(acetoxy-prop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate (Yield: 96.1 %).

Example 12:

Preparation of ethyl

6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate.

1.0 g of ethyl 3-(2-fluoroethylamino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate was dissolved in 8 ml of methyl ethyl ketone under heating to 75 ~ 80 ℃. 1.14 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 40 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 20 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 0.91g of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 96.8%).

Example 13:
Preparation of ethyl
6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate.

1.0 g of ethyl 3-(2-fluoroethylamino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate was dissolved in 8 ml of ethyl acetate under heating to 70 ~ 75 ℃. 1.14 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 40 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 20 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 0.9g of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 95.7%).

Example 14:
Preparation of ethyl

6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate.

1.0 g of ethyl 3-(2-fluoroethylamino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate was dissolved in 8 ml of EtOH under heating to 70 ~ 75 ℃. 1.14 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 1.5 hours. The reaction mixture was filtered under a reduced pressure and washed with 40 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 20 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 0.9g of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 95.7%).

Example 15:

Preparation of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate.

1.0 g of ethyl 3-(2-fluoroethylamino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate was dissolved in 8 ml of 1,2-dichloroethane under heating to 75 ~ 80 ℃. 1.14 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 3.0hours. The reaction mixture was filtered under a reduced pressure and washed with 40 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 20 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 0.89g of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 94.7%).

Example 16:

Preparation of ethyl

6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate.

1.0 g of ethyl 3-(2-fluoroethylamino)-2-(2,3,4,5-tetrafluorobenzoyl)acrylate was dissolved in 8 ml of toluene under heating to 75 ~ 80 ℃. 1.14 g (1.8 eq.) of K_3PO_4 was added in portions to the reaction mixture, which was then stirred at the same temperature for 6.0hours. The reaction mixture was filtered under a reduced pressure and washed with 40 ml of dichloromethane. The filtrate was concentrated under a reduced pressure. The resulting residue was dissolved in 20 ml of dichloromethane and then washed with water. The organic layer was concentrated under a reduced pressure to give 0.89g of ethyl 6,7,8-trifluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 94.7%).

Comparative Example 1:
Preparation of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate

3.0 g of ethyl 3-cyclopropylamino-2-pentafluorobenzoyl acrylate and 3.66 g (3.1 eq.) of anhydrous potassium carbonate were added to 22.2ml of N,N-dimethylformamide. The reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was concentrated under a reduced pressure to remove the solvent. 60 ml of dichloromethane was added to the resulting residue, which was then washed twice with 50 ml of water. The organic layer was dried over $MgSO_4$ and filtered under a reduced pressure. The resulting filtrate is concentrated under a reduced pressure to give 2.59g of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 91.5%).

Comparative Example 2:
Preparation of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate

The solution of 3.0g of ethyl 3-cyclopropylamino-2-pentafluorobenzoyl acrylate in 36.4ml of anhydrous tetrahydrofuran was cooled to 10 ℃. 0.41 g of 60 % sodium hydride was added to the reaction mixture, which was then stirred for 18 hours at room temperature. The reaction mixture was cooled to 5 ~ 10 ℃. 36.4ml of water is added to the reaction mixture, which was then stirred for 30 minutes. The organic layer was filtered under a reduced pressure and washed with water. The resulting wet cake was dried under a reduced pressure at 50 ℃ for 5 hours to give 2.01 g of ethyl 1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 71%).

Comparative Example 3:
Praparation of ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate.

The solution of 3.0 g of ethyl 3-cyclopropylamino-2-(2,6-dichloro-5-fluoropyridine-3-carbonyl)acrylate in 36.4ml of anhydrous tetrahydrofuran was cooled to 10 ℃. 0.36 g (1.05 eq.) of 60 % sodium hydride was added to the reaction mixture, which was then stirred for 18 hours at room temperature. The reaction mixture was cooled to 5 ~ 10 ℃. 36.4 ml of water was added to the reaction mixture, which was then stirred for 30 minutes. The organic layer was filtered under a reduced pressure and washed with water. The resulting wet cake was dried under a reduced pressure at 50 ℃ for 5 hours to give 2.34 g of ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (Yield: 87.3%).

Comparative Example 4:
Preparation of ethyl

1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carbox ylate.

The solution of 3.0 g of ethyl 2-(2,6-dichloro-5-fluoropyridine-3-carbonyl)-3-(2,4-difluorophenylamino)acrylate in 36.4 ml of anhydrous tetrahydrofuran was cooled to 10℃. 0.3 g (1.05 eq.) of 60 % sodium hydride was added to the reaction mixture, which was refluxed for 1 hour under N_2 gas. The reaction mixture was cooled to 5 ~ 10 ℃. 36.4ml of water was added to the reaction mixture, which was then stirred for 30 minutes. The organic layer was filtered under a reduced pressure and washed with water. The resulting wet cake was dried under a reduced pressure at 50 ℃ for 5 hours to give 2.33g of ethyl 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carbox ylate (Yield: 82.0 %).

Comparative Example 5:
Preparation of ethyl
1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate.

The solution of 3.0g of ethyl 2-(2-chloro-4,5-difluorobenzoyl)-3-cyclopropylamino acrylate in 12ml of 1,2-dimethyl-2-imidazolidinone was heated to 100~120℃. 1.76 g (1.4 eq.) of potassium carbonate was added to the reaction mixture, which was refluxed for 4 hours. The reaction was not completed (confirmed by TLC check).

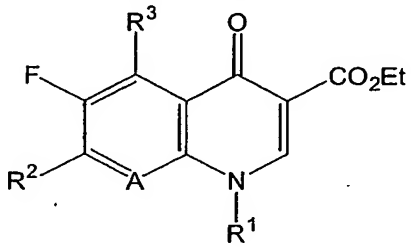
Comparative Example 6:
Preparation of ethyl
1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate.

The solution of 3.0 g of ethyl 2-(2-chloro-4,5-difluorobenzoyl)-3-(2,4-difluorophenylamino)acrylate in 30 ml of

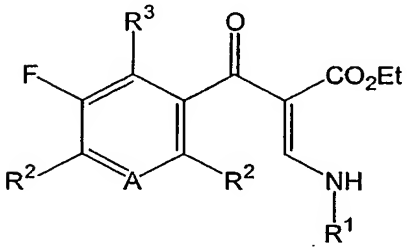
anhydrous tetrahydrofuran was cooled to 10 ℃. 0.3 g (1.02 eq.) of 60% sodium hydride was added to the reaction mixture, which was refluxed for 4.5 hours. The reaction mixture was cooled to 5 ~ 10 ℃. 54.6ml of water was added to the reaction mixture, which was then stirred for 30 minutes. The organic layer was filtered under a reduced pressure and washed with a mixed solution of *n*-hexane and ether (1/1). The resulting wet cake was dried under a reduced pressure at 40 ~ 45 ℃ for 6 hours to give 2.26 g of ethyl 1-(2,4-difluorophenyl)-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (Yield: 82.8%).

What is claimed is:

1. A process for preparing a compound of formula (I) or its salt, which comprises reacting a compound of formula (II) with potassium phosphate tribasic (K_3PO_4) in an orgarnic solvent:



(I)



(II)

wherein, R^1 is cyclopropyl, 2,4-difluorophenyl, or 1-acetoxyprop-2(S)-yl; R^2 and R^3 are independently hydrogen, chloro, or fluoro; and A is CH, CF, CNO_2, or N.

2. The process of claim 1, wherein the orgarnic solvent is selected from the group consisting of acetonitrile, methyl ethyl ketone, ethyl acetate, ethyl alcohol, dichloroethane, and toluene.

3. The process of claim 1, wherein amount of the potassium phosphate tribasic is 1.5 eq. ~ 2.8 eq. to 1 eq. of the compound of formula (II).

4. The process of claim 1, wherein the reacting is carried out at 60 ℃ ~ 85 ℃.

5. The process of claim 4, wherein the reacting is carried out at 75 ℃ ~ 80 ℃.

6. The process of claim 1, wherein the reacting is completed in about 1 ~ 12 hours.

7. The process of claim 6, wherein the reacting is completed in about 1 ~ 3 hours.

8. The process of any one of claims 1 through 7, further comprising a purifying step which comprises filtering a resulting product obtained from the process of any one of claims 1 through 7 to remove any by-product; concentrating the resulting filtrate; adding an organic solvent to the concentrate, followed by washing with water; and concentrating the resulting organic layer.

9. The process of claims 8, wherein the organic solvent is dichloromethane, ethyl acetate, or a mixture thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2003/002785

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 215/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D 215/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA online, NPS, Delphion Research Intellectual Property network database,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5869661 A (Chugai Seiyaku Kabushiki Kaisha) Feb. 9. 1999 (9. 2. 1999) see column 5	1-9
X	US 4599334 A (Bayer Aktiengesellschaft) Jul. 8. 1986 (8. 7. 1986) see column 5	1-9
A	US 2002/0120138 A1 (Bayer Aktiengesellschaft) Aug. 29. 2002 (29. 8. 2002) see whole document	1-9
A	US 5407932 A (Wakunaga Seiyaku Kabushiki Kaisha) Apr. 18. 1995 (18. 4. 1995) see whole document	1-9
A	US 4762844 A (Bayer Aktiengesellschaft) Aug. 9. 1988 (9. 8. 1988) see whole document	1-9

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 APRIL 2004 (19.04.2004)	20 APRIL 2004 (20.04.2004)

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